

20 December 2023

Roche-Genentech GENERATION HD2 Study updates & NEJM Publication

Dear Huntington's patient community leaders,

This year, we were fortunate enough to connect with many of you in person to discuss a variety of topics around the Phase II GENERATION HD2 study. We would like to take this opportunity to express our sincere gratitude for your ongoing collaboration and partnership throughout 2023. Your insights and perspectives are invaluable to us and, as always, we continually seek to apply your feedback and ensure that we put the needs of the Huntington's disease (HD) community at the forefront of our work.

Following your request to receive regular updates about our HD research efforts, and with 2023 coming to a close, we are keen to provide you with an update on the GENERATION HD2 study as well as inform you that the results from GENERATION HD1 have been published in the New England Journal of Medicine (NEJM).

GENERATION HD2 study update

- With study sites now activated in all countries and most sites recruiting, we are seeing a steady increase in enrolment. We are happy to share that to date approximately 50% of participants are enrolled across 69 centres in 15 countries: Argentina, Australia, Austria, Canada, Denmark, France, Germany, Italy, New Zealand, Poland, Portugal, Spain, Switzerland, UK, and the US.
- To ensure we continue to address the key priorities of this Phase II study, a small number of changes to the study protocol have been approved by the majority of the regulatory authorities. We do not make amendments to the protocol unless we deem them truly necessary and beneficial to the overall study design and study participants. In brief, the changes are as follows:
 - A reduction in the number of participants needed in the study from 360 to 300 participants
 - Removal of the HD-Integrated Staging System (HD-ISS) stage 2 and 3 criteria to avoid misclassification of participants, when used in conjunction with Diagnostic Confidence Level (DCL)
 - Additional minor changes in protocol language to ensure clarity
- The changes will only impact future recruitment efforts and will not impact any participants enrolled prior to the protocol being amended.

GENERATION HD1 results published in NEJM

- This month (December 2023), the full results from the GENERATION HD1 study were published in the [NEJM](#).



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- This study investigated two dosing regimens of tominersen: 120 mg every 8 weeks and 120 mg every 16 weeks. Those receiving 120 mg every 8 weeks had worse clinical outcomes and more adverse events compared to placebo. No differences were observed in the clinical outcomes or adverse event profiles of those receiving 120 mg every 16 weeks.
- The publication also reports the outcome of the exploratory post-hoc subgroup analysis¹ observing that tominersen may provide clinical benefit at lower doses in those who are younger with less advanced disease.
- As previously shared, this is why Roche/Genentech developed the Phase II GENERATION HD2 study that aims at evaluating safety, biomarkers and efficacy trends of tominersen at 100mg and 60mg every 16 weeks, relative to placebo, in people aged 25 to 50 with either very early subtle signs of HD, or early manifest HD.

The active involvement of the HD community has helped to shape this study and without your continued engagement we would not be where we are today. We thank you for your incredible support and for the dedication of the global HD community.

In 2024, we will continue to focus our efforts and resources to ensure we complete enrolment of the GENERATION HD2 study, enabling us to gain answers to the questions we all have, and progress the collective knowledge in Huntington's disease.

We wish you a restful and peaceful end of 2023, and look forward to sharing further updates on the study in the New Year.

Sincerely,

Flaminia Macchia, on behalf of the Roche & Genentech HD team
Global Patient Partnership Leader, Huntington's disease

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¹ Post-hoc analysis data should be interpreted with caution and need to be replicated in a randomised, placebo-controlled study.